REMARKS

The Office Action of October 3, 2002, presents the examination of claims 1-9 and 11-18. Claim 18 is canceled. Claims 1, 11-12, 14, and 16-17 are amended. No new matter is inserted into the application.

Specification

The Examiner objects to the specification for reciting the claims by number. In response to the Examiner's remarks, Applicants amend the specification to delete reference to claim numbers. Thus, the instant objection is overcome.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 18 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description. Claim 18 is canceled, thus rendering rejection thereof moot.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1, 3-9, and 11-18 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Claim 18 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the

pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 1, 14, and 17

Claims 1, 14, and 17 are rejected for a lack of antecedent basis for the phrase "said responsive transcriptional control factor" in step (c). Applicants amend the phrase to "said ligand-responsive transcriptional control factor" as suggested by the Examiner. Thus, the instant rejection is overcome.

Claims 11 and 12

The Examiner asserts that claims 11 and 12 are vague because it is unclear to which reporter gene (i.e., reporter gene (a) or reporter gene (c)) the claims refer. Applicants amend "reporter gene" to "reporter gene (a)" as suggested by the Examiner. Thus, the instant rejection is overcome.

Claim 16

The Examiner asserts that the recitation of "marker gene…which codes a phenotype…" is unclear, and suggests amending the claim to "marker gene…which encodes a polypeptide that confers a phenotype…." Applicants amend the claim in accordance

with the Examiner's suggestion. Thus, the instant rejection is overcome.

Claim 17

The Examiner asserts that the use of the term "substantially" in claim 17, with respect to the activity of the transcriptional control region, is indefinite. In order to overcome this rejection, "substantially" is deleted from the claim.

Applicants respectfully submit that the pending claims fully comply with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Bradfield '283 in view of Waldman et al.

The Examiner rejects claims 1, 3-9, 11, and 14-18 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Bradfield '283 (U.S. Patent 5,650,283), in view of Waldman et al. (*Analytical Biochemistry* 258:216-222(1998)). Claim 18 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Bradfield '283 generically teaches in section (v) that mammalian cells may be utilized in a GAL4 fusion approach with an expression plasmid encoding a chimeric Ah receptor (Ah activation domain and GAL 4 DNA binding domain) and with a reporter plasmid encoding an UAS_G element which binds to the chimeric Ah receptor. Bradfield '283 fails to teach that the cell thereof securely maintains the introduced DNA. Such teachings in Bradfield '283 also fail to describe specific methods which recover such cells that have the introduced DNA securely maintained therein. Furthermore, Bradfield '283 teaches in Example 6 as a representative example of said GAL4 fusion approach, that an expression plasmid and reporter plasmid are introduced to a host cell to provide a transient expression system. A transient expression system is very different from a cell securely maintaining the introduced DNA. One of ordinary skill in the art would know that a transient system provides a system that maintains, at best, the introduced DNA temporarily maintained in the cell. This is, of course, very different from a cell which has the introduced DNA securely maintained therein.

Further, Applicants respectfully point out that Bradfield '283 fails to specifically teach that the mammalian cells thereof can be utilized as a system utilizing a full-length Ah

receptor and a Dioxin Responsive Element. Such teachings in Bradfield '283 refer to the yeast cell thereof. On page 6, lines 11-13 of the Office Action, the Examiner writes that Bradfield '283 discloses, "The Ah receptor is maintained in the cell on a plasmid also containing a selectable marker, while the reporter gene is present on a second plasmid, but in the same molecule with a second selectable marker (see Figure 11)." In Bradfield '283, both the reporter gene and the second selectable marker (i.e., URA3, the gene for rescuing URA auxotrophy of yeast when the gene is expressed in yeast cells) exist on the same molecule. However, the plasmid is a plasmid for yeast gene engineering. The experimental system described in Bradfield '283 is designed for yeast. In contrast, the experimental system described in Waldman et al. as well as the invention of the present application are systems designed for animal cells. Accordingly, the Examiner fails to establish a motivation to combine Bradfield '283 and Waldman et al.

Furthermore, there is quite a difference between the yeast and the mammalian systems. There is no description in Bradfield '283 of "a minimum promoter which can function in an animal cell" which is recited in the instant claims, nor no teaching of this feature in the prior art. In addition, Bradfield '283

fails to describe a method for stable transfection into mammalian cells as noted above.

On page 7, lines 7-8 of the Office Action, the Examiner asserts, "Bradfield is modified by Waldman to encompass the stable transfection of mammalian cells with the system described above, thereby teaching all of the elements of claims 1, 3-9, 11, and 13-18." Applicants agree that Waldman et al. describes a method for the stable transfection of mammalian cells. However, there is no description or teaching in either Waldman et al. or Bradfield '283 of two specific features of the present invention. Specifically, neither reference teaches "a minimum promoter which can function in an animal cell" and "both the reporter gene and the second selectable marker exist on the same molecule." As noted above, Bradfield '283 does not describe the feature of a minimum promoter nor a method for stable transfection of mammalian cells. Waldman et al. also fails to describe the feature of a minimum promoter.

For the above reasons, Applicants respectfully submit that Bradfield '283 in view of Waldman et al. fails to render the present invention obvious. Withdrawal of the instant rejection is respectfully requested.

Bradfield '283 in view of Waldman et al. and further in view of Kushner '638

The Examiner rejects claims 2 and 12 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Bradfield '283, in view of Waldman et al., and further in view of Kushner '638 (U.S. Patent 6,117,638). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

On page 8, lines 8-12 of the Office Action, the Examiner states, "Kushner teaches a method for screening compounds in cells (including mammalian) that both activate (agonist) and block (antagonist) the stimulation of transcription of genes, some of which are regulated by hormone receptors, using a minimal promoter region comprised of a TATA box…." Applicants agree that Kushner '638 discloses a TATA box. However, Kushner '638 fails to make up for the deficiencies of Bradfield '283 and Waldman et al. Specifically, there is no description and no teaching relating to a "minimum promoter which can function in an animal cell" and "both the reporter gene and the second selectable marker exist on the same molecule." Both of these features of the present invention are recited in the instant claims.

Furthermore, Bradfield '283 discloses a plasmid for yeast gene engineering, which system is greatly different from a mammalian system as disclosed in Waldman et al. and Kushner '638. Thus, there is no motivation for the skilled artisan to combine Bradfield '283 with Waldman et al. and Kushner '638.

For the above reasons, Applicants respectfully submit that Bradfield '283 in view of Waldman et al., and further in view of Kushner '638 fails to render the present invention obvious. Withdrawal of the instant rejection is respectfully requested.

Conclusion

Applicants respectfully submit that the above remarks and/or amendments fully address and overcome the outstanding rejections and objections. For the foregoing reasons, Applicants respectfully request the Examiner to withdraw all of the outstanding rejections and objections, and to issue a notice of allowance indicating the patentability of the present claims. Early and favorable action of the merits of the present application is thereby respectfully requested.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the

Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at (703) 205-8000.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of three (3) months to April 3, 2003 in which to file a reply to the Office Action. The required fee of $930.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Version with Markings to Show Changes Made

MARKED UP VERSION SHOWING CHANGES MADE

IN THE SPECIFICATION

The specification from page 3, line 26, to page 8, line 19 is amended as follows:

The present invention provides:

[1.] an animal cell expressing a gene coding a ligand-responsive transcription control factor and securely maintaining a DNA comprising in a molecule, the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, in which said transcription control region substantially consists of a recognition sequence of said ligand-responsive transcription control factor and a minimum promoter which can function in said cell; and

(b) a selective marker gene which can function in said cell; provided that the following gene (c):

(c) a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control

factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a) is not present in said cell;

[2.] the cell according to the above [1], wherein said minimum promoter substantially consists of a TATA box;

[3.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is one selected from an aryl hydrocarbon receptor, intranuclear hormone receptor, estrogen receptor, androgen receptor and thyroid hormone receptor;

[4.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is an aryl hydrocarbon receptor;

[5.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is an intranuclear hormone receptor;

[6.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is an estrogen receptor;

[7.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is an androgen receptor;

[8.] the cell according to the above [1], wherein said ligand-responsive transcription control factor is a thyroid hormone receptor;

[9.] an animal cell expressing an aryl hydrocarbon receptor and an Arnt receptor, and securely maintaining a DNA comprising in a molecule, the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, wherein said transcription control region substantially consists of a recognition sequence of said aryl hydrocarbon receptor and a minimum promoter which can function in said cell and

(b) a selective marker gene which can function in said cell;

provided that the following gene (c):

(c) a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a)

is not present in said cell;

[10.] use of an animal cell [according to any one of the above 1 to 9] for evaluating an agonist activity or antagonist

activity of a chemical substance over the transcription promoting ability of a ligand-responsive transcription control factor, in a reporter assay measuring the amount of a reporter gene under transcription control of said ligand-responsive transcription control factor;

[11.] a method for evaluating a chemical substance to have agonist activity over the transcription promoting ability of a ligand-responsive transcription control factor, said method comprising:

(i) culturing an animal cell [according to any one of claims 1 to 9] in the presence of the chemical substance;

(ii) measuring the expression amount of a reporter gene in said cell and

(iii) assessing said chemical substance to have agonist activity over the transcription promoting ability of the ligand-responsive transcription control factor when the measured value of expression amount of said reporter gene introduced into said cell is larger than a measured value of expression amount of said reporter gene in the absence of said chemical substance;

[12.] a method for evaluating a chemical substance to have antagonist activity over the transcription promoting ability of

a ligand-responsive transcription control factor, said method comprising:

(i) culturing an animal cell [according to any one of claims 1 to 9] in the presence of the chemical substance and a ligand of said [ligand-reponsive] ligand-responsive transcription control factor;

(ii) measuring the expression amount of a reporter gene in said cell and

(iii) assessing said chemical substance to have antagonist activity over the transcription promoting ability of the ligand-responsive transcription control factor when the measured value of expression amount of said reporter gene introduced into said cell is smaller than a measured value of expression amount of said reporter gene in the presence of said ligand and the absence of said chemical substance;

[13.] a measuring kit comprising an animal cell [according to any one of the above 1 to 9];

[14.] a method for obtaining an animal cell for measuring the ability to control the activity of a ligand-responsive transcription control factor, said method comprising:

(i) introducing into an animal cell, a DNA comprising in a molecule the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, wherein said transcription control region substantially consists of a recognition sequence of said ligand-responsive transcription control factor and a minimum promoter which can function in said cell, and

(b) a selective marker gene which can function in said cell,

said animal cell being

an animal cell that comprises a DNA comprising a gene coding the ligand-responsive transcription control factor introduced thereto before, after or during the same time of above step (i) or that naturally having an ability to express the gene coding the ligand-responsive transcription control factor,

provided that a reporter gene (c) connected downstream from a promoter which transcription activity is unchanged by having said responsive transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which

can be differentiated from the protein coded by said gene (a), is not present in the cell; and

(ii) recovering from the transformed cell obtained from step (i), a transformed cell having said introduced DNA securely maintained therein;

[15.] the method according to the above [14], wherein said cell is an animal cell that comprises a DNA comprising a gene coding the ligand-responsive transcription control factor introduced thereto before, after or during the same time of the step (i);

[16.] the method according to the above [15], wherein the DNA comprising a gene coding the ligand-responsive transcription control factor, comprises in a molecule, a selective marker gene which can function in said cell and which codes a phenotype different from that of the gene (b).

IN THE CLAIMS

Claim 18 is canceled.

The following claims are amended:

1. (Amended) An animal cell expressing a gene coding a ligand-responsive transcription control factor and securely maintaining a DNA comprising in a molecule, the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, in which said transcription control region substantially consists of a recognition sequence of said ligand-responsive transcription control factor and a minimum promoter which can function in said cell; and

(b) a selective marker gene which can function in said cell;

provided that the following gene (c):

(c) a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive [responsive] transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a)

is not present in said cell.

11. (Amended) A method for evaluating a chemical substance to have agonist activity over the transcription promoting ability of a ligand-responsive transcription control factor, said method comprising:

(i) culturing an animal cell according to any one of claims 1 to 9 in the presence of the chemical substance;

(ii) measuring the expression amount of [a] reporter gene (a) in said cell and

(iii) assessing said chemical substance to have agonist activity over the transcription promoting ability of the ligand-responsive transcription control factor when the measured value of expression amount of said reporter gene (a) introduced into said cell is larger than a measured value of expression amount of said reporter gene (a) in the absence of said chemical substance.

12. (Amended) A method for evaluating a chemical substance to have antagonist activity over the transcription promoting ability of a ligand-responsive transcription control factor, said method comprising:

(i) culturing an animal cell according to any one of claims 1 to 9 in the presence of the chemical substance and a ligand of said [ligand-reponsive] ligand-responsive transcription control factor;

(ii) measuring the expression amount of [a] reporter gene (a) in said cell and

(iii) assessing said chemical substance to have antagonist activity over the transcription promoting ability of the

ligand-responsive transcription control factor when the measured value of expression amount of said reporter gene (a) introduced into said cell is smaller than a measured value of expression amount of said reporter gene (a) in the presence of said ligand and the absence of said chemical substance.

14. (Twice Amended) A method for obtaining an animal cell for measuring the ability to control the activity of a ligand-responsive transcription control factor, said method comprising:

(i) introducing into an animal cell, a DNA comprising in a molecule the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region, wherein said transcription control region substantially consists of a recognition sequence of said ligand-responsive transcription control factor and a minimum promoter which can function in said cell, and

(b) a selective marker gene which can function in said cell,

said animal cell being

an animal cell that comprises a DNA comprising a gene coding the ligand-responsive control factor introduced

thereto before, after or during the same time of above step (i) or that naturally has an ability to express the gene coding the ligand-responsive transcription control factor,

provided that a reporter gene (c) connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive [responsive] transcription control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a), is not present in the cell; and

(ii) recovering from the transformed cell obtained from step (i), a transformed cell having said introduced DNA securely maintained therein.

16. (Amended) The method according to claim 15, wherein the DNA comprising a gene coding the ligand-responsive transcription control factor, comprises in a molecule, a selective marker gene which can function in said cell and which encodes a polypeptide

that confers [codes] a phenotype different from that of the gene (b).

17. (Twice Amended) An animal cell expressing a gene coding a ligand-responsive transcription control factor and securely maintaining a DNA comprising in a molecule, the following genes (a) and (b):

(a) a reporter gene connected downstream from a transcription control region; wherein said transcription control region contains a minimum promoter and a recognition sequence of the ligand-responsive transcription control factor and contains no sequence having the transcription control ability [substantially] changed by the ligand-responsive transcription control factor recognition sequence and minimum promoter; and

(b) a selective marker gene which can function in said cell;

and provided that the following gene (c):

(c) a reporter gene connected downstream from a promoter which transcription activity is unchanged by having said ligand-responsive [responsive] transcription

control factor contacted with a ligand of said ligand-responsive transcription control factor, said reporter gene (c) coding a protein which can be differentiated from the protein coded by said gene (a)

is not present in said cell.